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Population-based trends in pregnancy hypertension and preeclampsia: An international comparative study

Running head: International trends in preeclampsia

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ABSTRACT

Objective: The objective of this study was to compare international trends in overall pregnancy hypertension (including gestational hypertension, preeclampsia and eclampsia) rates and in preeclampsia alone.

Design: Population data (from birth and/or hospital records) on all women giving birth were available from Australia (2 states), Canada (Alberta), Denmark, Norway, Scotland, Sweden and the USA (Massachusetts) for a minimum of 6 years from 1997-2007. All countries used the 10th revision of the *International Classification of Diseases (ICD),* except the USA which used the 9th revision. There were no major changes to the diagnostic criteria or methods of data collection in any country during the study period. Population characteristics as well as rates of pregnancy hypertension and preeclampsia were compared.

Results: Absolute rates varied across the populations as follows: pregnancy hypertension (3.6% to 9.1%), preeclampsia (1.4% to 4.0%) and early onset preeclampsia (0.3% to 0.7%). Pregnancy hypertension and/or preeclampsia rates declined over time in most countries. This was unexpected given that factors associated with pregnancy hypertension such as pre-pregnancy obesity and maternal age are generally increasing. However, there was also a downward shift in gestational age with fewer pregnancies reaching 40 weeks.

Conclusion: The rate of pregnancy hypertension and preeclampsia decreased in northern Europe and Australia from 1997 to 2007, but increased in the USA. Use of a different ICD coding version in the USA may contribute to the difference in trend. Elective delivery prior to the due date is the most likely explanation for the decrease observed in Europe and Australia. As well, use of interventions that reduce the risk of pregnancy hypertension and/or progression to preeclampsia (low-dose aspirin, calcium supplementation and early delivery for mild hypertension) may have contributed to the decline.

ARTICLE SUMMARY

Article focus

- The population prevalence of factors associated with increased and decreased risk of pregnancy hypertension and preeclampsia have changed over time, but the impact of these changes is unknown
- International comparisons of *absolute population rates* of pregnancy hypertension and preeclampsia are hindered by different diagnostic criteria and methods of data collection
- Comparing *trends* between countries overcomes the difficulties in comparing absolute rates.

Key message

- Pregnancy hypertension and/or preeclampsia rates declined over time in northern Europe and Australia but not the USA
- Declining hypertension rates were accompanied by a downward shift in gestational age with fewer pregnancies reaching term, the time when the pregnancy hypertension and preeclampsia are most likely to occur

Strengths and limitations

- Strengths include numerous validation studies indicating that the hypertensive disorders are reliably reported in the population data sets used for the study and the consistency of trends across most countries
- Limitations include a different ICD coding version in the USA and lack of available information on clinical interventions

INTRODUCTION

Hypertension complicates up to 10% of all pregnancies and is associated with increased risk of adverse fetal, neonatal and maternal outcomes, including preterm birth, intrauterine growth restriction, perinatal death, acute renal or hepatic failure, antepartum haemorrhage, postpartum haemorrhage and maternal death [1, 2]. Pregnancy hypertension (also known as pregnancy-induced or pregnancy-associated hypertension) has its onset from 20 weeks of gestation and ranges from hypertension alone (gestational [non-proteinuric] hypertension) through proteinuria and multi-organ dysfunction (preeclampsia) to seizures (eclampsia) [3-5]. Preeclampsia may be superimposed on pre-existing chronic hypertension. Although preeclampsia represents the severe end of the spectrum, women with any form of pregnancy hypertension are at increased risk of adverse outcomes [6, 7].

Risk factors for pregnancy hypertension and preeclampsia have been well documented [2, 7-13]. Factors that increase risk include nulliparity, older maternal age, multiple births, diabetes, chronic hypertension, obesity, previous preeclampsia, family history of preeclampsia, a new partner and/or ≥10 years since last pregnancy, renal disease, and the presence of antiphospholipid antibodies [2, 7-9, 11, 13, 14]. Decreased risk of pregnancy hypertension and preeclampsia has been associated with placenta praevia, smoking (although smoking may only be protective in the non-obese), summer births, low-dose aspirin and calcium supplementation in high-risk women, treatment of gestational diabetes and use of anti-hypertensive medications [2, 9, 10, 12, 15-19]. As the majority of cases of pregnancy hypertension and preeclampsia occur at term, increasing rates of early elective delivery may reduce their frequency [20-23]. Trends in pregnancy hypertension and preeclampsia are the result of the effects of changes in all these factors.

Population rates of pregnancy hypertension (based on routinely collected data) vary substantially in high-income countries, ranging from 4% to 10%, including preeclampsia rates of 2% to 5% [7, 11, 24-28]. At least part of this variation is likely due to under-ascertainment and/or misclassification of gestational hypertension and preeclampsia [29].

There are few recent reports of population trends in pregnancy hypertension [26-28]. International comparisons of *absolute population rates* of pregnancy hypertension and preeclampsia have been considered "virtually impossible" because of different diagnostic criteria and methods of data collection [30]. However, comparing *trends* between countries overcomes the difficulties in comparing absolute rates. Provided that methods of reporting do not change from year-to-year, temporal variations in each country reflect true changes in that country's rate of hypertension. The aim of this study was to determine and compare population-based trends in pregnancy hypertension and preeclampsia in high income countries.

METHODS

We used population health data (record-linked birth and hospital data where available) to determine pregnancy hypertension and preeclampsia rates in Australia, Canada, Denmark, Norway, Scotland, Sweden and the USA. We pre-specified that (1) participating centres had to provide a minimum of 6 years of data in the period from 1997 to 2007, and (2) if coding of hypertension was based on the *International Classification of Diseases (ICD),* the same ICD version had to be used for the entire period. The latter stipulation was made because preeclampsia coding in ICD-9 and ICD-10 are not comparable.

Study populations and data sources

The study populations included all women who gave birth (both live births and stillbirths) during the study period. Eight collaborating centres provided population health data on a regional or national basis, including: Australia (the states of New South Wales [NSW] and Western Australia [WA]), Canada (province of Alberta); Denmark, Norway, Scotland, Sweden and the USA (state of Massachusetts). Table 1 provides the average population, number of births and information on the data sources in the 8 study areas. With the exception of the USA, all participating countries have universal health coverage for maternity care provided by midwives, general practitioners and obstetricians. Australia also has a parallel private health care system similar to that in the USA; about one-third of women seek private obstetric care.

Population health data were obtained from birth and/or hospital records in each study area. Birth data including information on maternal characteristics, pregnancy, labour, delivery and infant outcomes were collected by the attending midwife or doctor in a standard format. In Scotland, clinical coding staff within each hospital's medical records department extracted the birth data from all available medical records. Hospital data included demographic, administrative, and clinical data for all hospital discharges. Diagnoses and procedures for each admission were coded from the medical records according to the ICD. The number of diagnosis fields available in each medical record varied by study area, ranging from 6 to 25 (Table 1). However, a consistent numbers of fields were used within each country over the time period of the study.

Record-linked birth and hospital data were utilised in Australia, Denmark and the USA. In Denmark the availability of a unique identifier allows unambiguous, deterministic linkage of

records for each woman. In Australia and the USA, probabilistic linkage uses variables such as name, date of birth and address to match records for individual women, and achieves linkage rates of ~98%.

Primary outcomes: pregnancy hypertension and preeclampsia

Population health data from each collaborating centre were used to estimate the overall incidence of any pregnancy hypertension (gestational hypertension, preeclampsia or eclampsia) and preeclampsia. During the study period, gestational hypertension was defined as the *de novo* onset of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) from 20 weeks' gestation onwards and preeclampsia as the *de novo* onset of hypertension from 20 weeks' gestation onwards accompanied by proteinuria [3].

Information on maternal hypertension status was available from birth and/or hospital data (Table 1). In the birth data, gestational hypertension, preeclampsia (in some cases by severity) and eclampsia data were generally collected as check-box fields and/or free text fields that were coded according to the ICD. In all hospital data, hypertension was coded from the medical record according to the ICD. Because of expected variations in reporting and/or coding we made an *a priori* decision that the identification of pregnancy hypertension and preeclampsia would be based on validation studies and each collaborating group's own best method for ascertaining these conditions. Since we focused on trends over time, our key concern was to ensure that data collection and reporting within each country were consistent over the study period. It was clear that differences in the baseline rates between regions would be unavoidable.

Validation studies focusing on reporting of hypertensive disorders of pregnancy in birth and hospital data from Europe, North America and Australia have had remarkably consistent findings: pregnancy hypertension and preeclampsia reliably and accurately reported in population health data [31]; ascertainment is improved when hypertension is identified from more than one data source (birth and hospital records for the birth admission or birth and antenatal records) [29, 32]; preeclampsia is generally better ascertained and more accurately reported than gestational hypertension [24, 25, 29]; the broad category of 'any preeclampsia' is more reliably reported than subgroups stratified by severity [33, 34]; similarly the broad category of pregnancy hypertension is more accurately reported than the subgroups of preeclampsia and gestational hypertension, with the possible exception of countries where ascertainment of gestational hypertension is known to be low (including Denmark and Sweden) [24, 29, 34, 35].

Exposures

The collaborating centres provided information on maternal and pregnancy characteristics of the study populations including age, parity, smoking at registration and/or during pregnancy, ethnicity, overweight/obesity (BMI ≥25.00 kg/m^2), diabetes, chronic hypertension, multiple gestation, induction of labour, mode of delivery and gestational age. Preterm birth (<37 weeks gestation) was categorised as spontaneous or elective (planned/elective caesarean section before the onset of labour or induced labour). Gestational age was reported in completed weeks, based on the best available estimate from ultrasound dating and/or menstrual history. The most reliable source (birth and/or hospital data) was used to determine exposures.

Approvals

The Publication Board at the Medical Birth Registry of Norway and the Danish Registry Board approved the study. In NSW, the record linkage was approved by the NSW Population and Health Services Research Ethics Committee (2006-06-011). No other permissions were required for analysis and presentation of the data.

Statistical Analyses

All analyses were based on women who delivered in each study location. We plotted secular trends in pregnancy hypertension and preeclampsia (per 100 deliveries per annum) for each study area based on available data over the study period. Temporal trends in numbers of pregnancy hypertension and preeclampsia events by study area were modelled using negative binomial regression. The covariance matrix was scaled by the deviance divided by the degrees of freedom and the additional variance component *k* estimated by maximum likelihood. Study year was fitted to the models, permitting estimation of yearly changes (with associated 95% confidence intervals) in numbers of events relative to baseline. Model fit (P>0.2 in all models) was assessed using the Pearson chi-squared goodness of fit statistic. Changes over time in population characteristics were analysed using the chi-squared test for trend with the significance level set at P<0.01.

RESULTS

Data were available from the 8 study areas for periods of 6 to 10 years between 1997 and 2007. The maternity populations ranged in size from an average of 25,000 per annum (pa) in Western Australia to 100,000 pa in Sweden (Table 1). Although not measured from the same starting time or for the same duration, significant changes in the number of women giving birth were observed in some areas, with increases in Alberta (by 26%), Sweden (+17%) and Australia (+7%), and declines in Scotland (–6%), Denmark (–4%) and Massachusetts (–4%).

In Norway, deliveries declined from 1999 to 2002 (–6%) and then gradually returned to baseline in 2006.

Details of maternal and pregnancy characteristics and trends for each population are presented in Table 2, highlighting some differences between study areas. The proportion of women delivering their first baby ranged from 40.7% in Norway to 45.2% in Scotland, and increased in all populations. Multiple gestation rates were higher in Massachusetts, which also had the highest proportion of mothers aged ≥35 years. The Nordic countries (Denmark, Norway and Sweden) had lower rates of deliveries among teenagers, comparatively low rates of medical induction and operative deliveries (vaginal instrumental and caesarean deliveries), and lower rates of preterm birth. Maternal age increased over time in the Nordic countries, Australia and Scotland. Smoking declined, and inductions and caesarean sections increased in most study areas. Where data were available, there was a downward shift in gestational age at term with an increasing proportion of infants born at 37-39 weeks. This was accompanied by an increase in preterm births in NSW and Denmark. Information on the proportion of women who were overweight or obese was only available in Sweden (35.5%) and Denmark (32.1%). In Sweden BMI information was available for 86% of women and in Denmark data were available for 92% of women for 2004-2006, with no significant change in the rate of overweight or obesity during that period.

As anticipated, the reported rates of pregnancy hypertension (3.6% to 9.1%), preeclampsia (1.4% to 4.0%) and early onset preeclampsia (0.3% to 0.7%) varied between study areas. The contribution of preeclampsia to the pregnancy hypertension rate also varied from 23% in Alberta to 74% in Sweden (median=41%).

Figure 1 shows the trends in pregnancy hypertension rates for each study area. The average yearly rate decreased significantly during the study periods in 4 of the 8 areas. In Scotland pregnancy hypertension decreased by -6.2% per annum (pa) (95% CI -5.2%, -7.3%), in WA by -4.8% pa (95% CI -4.1%, -5.5%), in NSW by -4.1% pa (95% CI -3.4%, -4.8%), and in Sweden by -0.6% pa (95% CI -0.1%, -1.1%). There was no significant change in the rate of pregnancy hypertension in Alberta (p=0.43), Denmark (P=0.23) or Norway (P=0.90), while in Massachusetts the rate increased significantly by 2.3% pa (95% CI 1.9%, 2.7%)

Trends in preeclampsia (Figure 2) mirrored those of pregnancy hypertension in most study areas with significant decreases in NSW [-6.0% pa (95% CI: -4.2%, -7.7%)], Scotland [-3.0% pa (95% CI: -0.7%, -5.2%)], WA [-1.3% pa (95% CI: -0.3%, -2.3%)], and Sweden [-1.2% pa (95% CI: -0.6%, -1.8%). A significant increase was observed in Massachusetts [2.4% pa (95% CI: 1.5%-3.3%)]. Norway and Denmark experienced declines in preeclampsia rates [-2.5% pa (95% CI: -1.4%, -3.5%) and -0.7% pa (95% CI: -0.02%, -1.4%), respectively], despite the lack of significant reductions in pregnancy hypertension. In Alberta, the preeclampsia rate increased by 4.4% pa (95% CI: 2.4%-6.4%), albeit from a very low base rate of 1.1%. Where data were available, the trends in pregnancy hypertension and preeclampsia were similar when analyses were restricted to nulliparous women.

DISCUSSION

Most countries saw a decline in the rates of pregnancy hypertension and/or preeclampsia over time. This was an unexpected result since factors thought to be positively associated with pregnancy hypertension such as pre-pregnancy overweight and obesity, diabetes, multiple births, and maternal age are generally recognised as increasing while smoking during pregnancy (associated with reduced rates of pregnancy hypertension) has decreased. Trends in

these factors have been proposed as possible explanations for the increase in pregnancy hypertension and preeclampsia rates reported for the entire USA from 1987 to 1998 (although the rates plateaued from 1999 to 2004) [26]. In contrast, a study from Western New York based on a perinatal database from 1999 to 2003 reported significant declines in both pregnancy hypertension and preeclampsia [27].

As expected, we observed variation between study areas in baseline rates - more marked for pregnancy hypertension than for preeclampsia. However, for study areas with declining rates, the rates tended to converge over time. A significant part of the variation in baseline rates was likely related to differences in study population inclusion criteria and data recording methods. Although the lower gestational age boundary varied by country (gestational age 20-22 weeks or birth weight 350-500 g for live births and 20-28 weeks for stillbirths), the impact was likely to be small as pregnancy hypertension and preeclampsia most frequently occur in the third trimester [7, 27, 36]. Stillbirth, a complication of preeclampsia, is counted only from 28 weeks onwards in the Swedish data which may have reduced the country's rates. However, the number of stillbirths <28 weeks was low (<2/1,000 births) and similar hypertension rates in Denmark (which included stillbirths in earlier weeks) argues against this as a significant explanation for observed differences in pregnancy hypertension rates. At the same time, validation studies from Denmark and Sweden indicated under-enumeration of gestational hypertension compared with preeclampsia, which would explain the high ratio of preeclampsia to gestational hypertension in these countries [24, 25].

The period of available data is another factor influencing the pregnancy profiles. For example, caesarean section rates tended to be lower in countries reporting for longer time periods;

shorter, more recent periods have the highest rates. In addition, national guidelines for defining preeclampsia differ with respect to the inclusion or exclusion of non-proteinuric hypertension with multi-organ disease [2, 3]. Inclusion of non-proteinuric hypertension in Australia could have increased the incidence of preeclampsia by up to 25%, but should not have affected the overall rate of pregnancy hypertension [36].

Finally, hospital data in all study areas, except the USA, were coded using the 10th revision of the ICD. Unlike ICD-9, ICD-10 combines mild preeclampsia with gestational hypertension. While this should not affect the reported rate of pregnancy hypertension, it reduces the rate of preeclampsia in ICD-10 compared with ICD-9. The change in NSW from ICD-9 in 1997 to ICD-10 in 1998 coincided with a shift from an increasing to a decreasing trend in pregnancy hypertension, suggesting the impact of the ICD version should not be disregarded. Furthermore, study areas with the highest rates of pregnancy hypertension (Australia and USA) have linked data and more diagnosis fields per record, characteristics shown to increase ascertainment in population data [29, 32]. Combinations of all these factors, as well as differences in the population of pregnant women are likely contributors to differences in baseline rates between the study areas.

Although inconsistencies in diagnostic criteria, study populations, and temporal, geographic and demographic factors may explain differences in baseline rates, they do not explain the observed trends in pregnancy hypertension and preeclampsia. The year-to-year trends are influenced by the prevalence of risk factors in the study populations, prenatal care and therapeutic interventions. Many recognised risk factors for pregnancy hypertension and preeclampsia increased in all or some of our study populations during the study period,

including nulliparity, advanced maternal age, diabetes, chronic hypertension and multiple pregnancy, while smoking rates (an apparent protective factor) declined everywhere. Diabetes, chronic hypertension and multiple pregnancy are associated with a 2- to 3-fold increase in risk of preeclampsia, but occur infrequently [2, 9]. Small changes in the prevalence of these factors are unlikely to have a large impact on pregnancy hypertension rates in the population. While advanced maternal age and obesity are more common, the magnitude of risk is lower (less than double) [2, 9]. Although only a few countries could provide information on obesity in pregnant women, we assume that this is increasing in all participating countries, based on population trends.

Nulliparity provides perhaps the most contrary and puzzling disparity in preeclampsia trends. Nulliparity is common (42%-45%, increasing in most populations) and has a relative risk of preeclampsia estimated at 2.9 (95% CI 1.3-6.6) [9]. However, in our study, overall nulliparity rates did not correlate with the preeclampsia rates as expected. Instead, Scotland had both the lowest preeclampsia rates and the highest nulliparity rate, and Norway had the highest preeclampsia rates and the lowest nulliparity rate. Furthermore, the trends observed for all women were also observed amongst nullipara. Among multipara, preeclampsia in a prior pregnancy has been associated with a 7-fold increased risk in a subsequent pregnancy [9]. Although women with preeclampsia are also less likely to have another pregnancy, this does not explain the lower overall risk of preeclampsia in parous women [11]. Consequently, the impact of trends in parity on the population rates is complex and difficult to predict.

Changes in elective delivery (labour induction and caesarean section) are changing the distribution of gestational age at or near term. Increasing rates of early elective delivery before 40 weeks gestation have been reported internationally [20, 22, 23]. Almost 90% of

pregnancy hypertension and over 70% of preeclampsia events occur at term, but fewer pregnancies are reaching 40 weeks or beyond [7, 27, 36]. Increasing rates of planned delivery of women with gestational hypertension could also explain why more study areas had decreases in preeclampsia rates [21]. Reducing the median length of gestation by even a few days could mean that a substantial number of women now deliver before they become hypertensive. It is also possible that utilisation of interventions that reduce the risk of pregnancy hypertension and/or progression to preeclampsia (such as low-dose aspirin and calcium supplementation) are contributing to the decline in hypertension rates [15, 18].

A strength of our study is the quality of information collected from very different health systems. While variation may occur in reporting, completeness and validity of data, there were no major changes in data collection or reporting methods during the study period. Validation studies of the reporting of hypertension in pregnancy have been conducted in Australia, Canada, Denmark, Norway, Sweden and the USA with consistent findings about the reliability of each country's ascertainment methods [24, 25, 29, 33-35, 37]. This consistency is important when examining year-to-year variation.

In conclusion, we found declining rates of pregnancy hypertension and preeclampsia in northern Europe and Australia, a reassuring finding in the context of increasing maternal age, nulliparity and obesity. However, an increase in these rates was observed in the USA. It is unclear whether the different ICD coding version used in the USA played a role in this finding. The role of elective delivery prior to the due date (especially late preterm and early term) in limiting the period of gestation during which the pregnancy hypertension and preeclampsia risks are greatest warrants further investigation.

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Competing interests statement

The authors declare that they have no competing interests.

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Authors' contributions

CLR and JBF conceived the project and developed the idea in collaboration with JMM, JC, JEN, JN, CJW. All authors (CLR, JBF, CSA, SA, JC, SC, MG, MK, KKM, AL, CM, JMM, NN, JEN, JN, HTS, RW, CJW) contributed to study design, CLR, JC, SC, MK, KMM, NN, HTS and RW were responsible for data acquisition and CSA, SA, SC, MG, KKM, AL, CM, RW, CJW contributed to the analysis of data. CLR and JBF initially drafted the manuscript and all authors (CLR, JBF, CSA, SA, JC, SC, MG, MK, KKM, AL, CM, JMM, NN, JEN, JN, HTS, RW, CJW) were involved in critical revision of the intellectual content. All authors (CLR, JBF, CSA, SA, JC, SC, MG, MK, KKM, AL, CM, JMM, NN, JEN, JN, HTS, RW, CJW) approved the final manuscript.

Data Sharing Statement

The data are not available for sharing.

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Table 1: Population, birth numbers and data sources by study area

Maternal and pregnancy factors	Alberta Canada	NSW Australia	WA Australia	Denmark	Norway	Scotland	Sweden	Massachusetts USA
Total population	3.7 million	7.0 million	2.2 million	5.5 million	4.9 million	5.1 million	9.2 million	6.5 million
Births per annum	~42,000	~90,000	~25,000	~66,000	~60,000	~58,000	~100,000	~80,000
Inclusion criteria	Live and stillbirths ≥20 wks	Live and stillbirths ≥20 wks or ≥400g	Live and stillbirths ≥20 wks or ≥400g	Live and stillbirths ≥22 wks	Live and stillbirths ≥22 wks or ≥500g	Live and stillbirths	Live births ≥22 wks Stillbirths ≥28 wks	Live and stillbirths >20 wks or >350 g
Source of population data	DAD (H), BRVS (B)	APDC (H), MDC (B)	HMDS (H), MNS (B)	DNRP DMBR	MBRN CPRN	SMR02	SMBR	PELL
Linkage method	NA	Probabilistic	Probabilistic	Deterministic	Deterministic	NA	NA	Probabilistic
Source of hypertension data	H	B and/or H	B and/or H	H	B	B	B	B and/or H
No. of diagnosis fields for hypertension reporting (data source)	25 (H)	11 (H) Checkbox(B)	21 (H) Checkbox(B)	20 (H)	Check-boxes and free text (B)	6 (B)	12 (B)	15 (H) Check-box (B)
ICD version	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-9
ICD codes for hypertension Pregnancy hypertension - Preeclampsia	 O11, O13-16 O11, O14-15	 O11, O13-16 O11, O14-15	 O11, O13-16 O11, O14-15	 O11, O13-15 O11, O14-15	 O11, O13-15 O11, O14-15	 O11, O13-16 O11, O14-15	 O11, O13-16 O11, O14-15	 642.3-642.9 642.4-642.6

H= Hospital data; B=Birth or obstetric data, NA=Not Applicable

DAD= Discharge Abstract Database; BRVA= Birth Registry of Vital Statistics; APDC=Admitted Patient Data Collection, MDC=Midwives Data Collection; HMDS=Hospital Morbidity Data System; MNS=Midwives' Notification System; DNRP=Danish National Registry of Patients; DMBR= Danish Medical Birth Registry MBRN=Medical Birth Registry of Norway; CPRN= Central Population Registry in Norway; SMR02=Scottish Morbidity Record 2; SMBR= Swedish Medical Birth Register; PELL= Pregnancy to Early Life Longitudinal Data System

Table 2: Population characteristics by study area

Maternal and pregnancy factors	Alberta Canada N=256,137 %	NSW Australia N=732,288 %	WA Australia N=149,624 %	Denmark N=645,993 %	Norway N=456,353 %	Scotland N=531,622 %	Sweden N=913,779 %	Massachusetts USA N= 762,723 %
Study period	2002-2007	1998-2006	2000-2005	1997-2006	1999-2006	1997-2006	1997-2006	1998-2007
Maternal age (years								
<20	5.8	4.3†	4.6†	1.6†	2.4	8.3†	1.8	6.5
20-34	79.5	76.7†	75.2†	82.6	81.7	74.6†	80.1	71.5
≥35	14.7	19.0*	20.2*	15.8*	15.9*	17.1*	18.1*	22.0
Nullipara	44.2*	41.6*	41.6*	42.9*	40.7*	45.2*	43.9*	44.6
Multiple births	1.6[1]	1.6*	1.7	1.5*	1.9	1.5	1.5†	2.3
Diabetes (any)	4.0	5.4*	4.3	1.7*	1.5*	0.8	1.3	5.3
- Gestational diabetes	3.5	5.0*	3.8	1.3	0.8*	0.5	0.9	4.4
- Pre-existing DM	0.5	0.4*	0.6	0.4	0.7*	0.4	0.4*	1.0
Chronic hypertension	0.4	1.2*	1.1	0.4*	0.6†	0.3	0.5*	1.6
Smoking	Not available	17.4†	19.3†	20.6[2]†	18.6[3]† 13.1[4]†	24.8†	10.7[5]†	12.3
Induction of labour	21.4†	24.6*	29.2*	12.4*	12.0*	25.8	17.8*	20.1
Mode of delivery								
- Normal vaginal	61.4†	64.8†	57.6	75.7†	77.3	65.3†	76.8†	66.5
- Instrumental	13.0†	10.4†	12.4	7.2*	8.1*	12.5	7.5	6.1
- Caesarean section	25.6*	24.7*	30.0*	17.1*	14.8*	22.2*	15.7*	27.4
Term births								
-≥40 weeks	40.1	49.6†	43.6†	54.1†	53.6†	54.4†	53.5†	
- 37-39 weeks	51.2	43.9*	48.8*	39.4*	40.0*	38.6*	40.8*	
Preterm births (all)	8.4	6.5*	7.6	6.5*	6.4	7.0	5.5	9.5
- elective –see below	2.5	2.5*	3.6*	1.3*	2.8	0.6[7]	1.6	Not available
- spontaneous	5.9	4.0	4.0	5.2	3.6	6.4	3.9*	
OUTCOMES								
Any pregnancy hypertension	6.0†	8.8†	9.1†	3.6	5.8	5.9†	3.9†	7.0*
- preeclampsia	1.4*	3.1†	2.9†	2.7†	4.0†	2.2†	2.9†	3.3*
- preeclampsia ≤34 wks	0.7[6]	0.3	0.6	0.3	0.4	0.3	0.4	0.6

Percentages may not add to 100 because of missing data.
* increasing and † decreasing over the study period, χ^2 for trend P<0.01; 1. Alberta – multiple birth data available for 98.5% of women; 2. Denmark – smoking data available for 96% of women; 3. Norway – daily smoking in the first trimester (available for 83% of women); 4. Norway – daily smoking in the last trimester (available for 78% of women); 5. Sweden –smoking data available for 93% of women; 6. Alberta – gestational age available for 2004-2007; 7. Scotland – elective caesarean sections only

Figure legends

Figure 1: International trends in pregnancy hypertension

Figure 2: International trends in preeclampsia

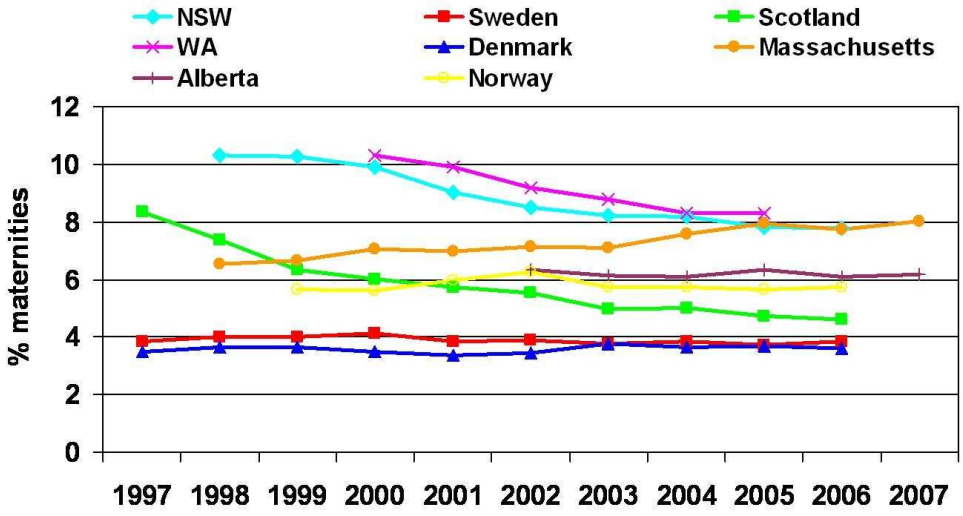
STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7, 22,24
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-8, 22
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8,22
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	NA (population data)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	24
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA (population data)

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	22-23
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	24
		(b) Indicate number of participants with missing data for each variable of interest	23
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10, 24
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figures 1 and 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



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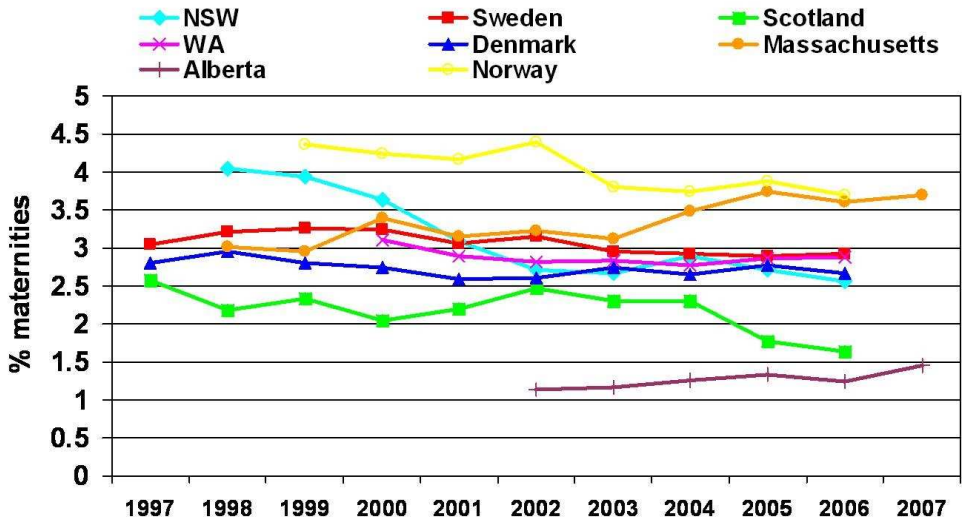

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Population-based trends in pregnancy hypertension and preeclampsia: An international comparative study

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Population-based trends in pregnancy hypertension and preeclampsia: An international comparative study

Running head: International trends in preeclampsia

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ABSTRACT

Objective: The objective of this study was to compare international trends in preeclampsia rates and in overall pregnancy hypertension rates (including gestational hypertension, preeclampsia and eclampsia).

Design: Population data (from birth and/or hospital records) on all women giving birth were available from Australia (2 states), Canada (Alberta), Denmark, Norway, Scotland, Sweden and the USA (Massachusetts) for a minimum of 6 years from 1997-2007. All countries used the 10th revision of the *International Classification of Diseases (ICD),* except Massachusetts which used the 9th revision. There were no major changes to the diagnostic criteria or methods of data collection in any country during the study period. Population characteristics as well as rates of pregnancy hypertension and preeclampsia were compared.

Results: Absolute rates varied across the populations as follows: pregnancy hypertension (3.6% to 9.1%), preeclampsia (1.4% to 4.0%) and early onset preeclampsia (0.3% to 0.7%). Pregnancy hypertension and/or preeclampsia rates declined over time in most populations. This was unexpected given that factors associated with pregnancy hypertension such as pre-pregnancy obesity and maternal age are generally increasing. However, there was also a downward shift in gestational age with fewer pregnancies reaching 40 weeks.

Conclusion: The rate of pregnancy hypertension and preeclampsia decreased in northern Europe and Australia from 1997 to 2007, but increased in Massachusetts. Use of a different ICD coding version in Massachusetts may contribute to the difference in trend. Elective delivery prior to the due date is the most likely explanation for the decrease observed in Europe and Australia. As well, use of interventions that reduce the risk of pregnancy hypertension and/or progression to preeclampsia (low-dose aspirin, calcium supplementation and early delivery for mild hypertension) may have contributed to the decline.

ARTICLE SUMMARY

Article focus

- The population prevalence of factors associated with increased and decreased risk of pregnancy hypertension and preeclampsia have changed over time, but the impact of these changes is unknown
- International comparisons of *absolute population rates* of pregnancy hypertension and preeclampsia are hindered by different diagnostic criteria and methods of data collection
- Comparing *trends* between countries overcomes the difficulties in comparing absolute rates.

Key message

- Pregnancy hypertension and/or preeclampsia rates declined over time in northern Europe and Australia but not Massachusetts (USA)
- Declining hypertension rates were accompanied by a downward shift in gestational age with fewer pregnancies reaching term, the time when the pregnancy hypertension and preeclampsia are most likely to occur

Strengths and limitations

- Strengths include numerous validation studies indicating that the hypertensive disorders are reliably reported in the population data sets used for the study and the consistency of trends across most countries
- Limitations include a different ICD coding version in Massachusetts and lack of available information on clinical interventions

INTRODUCTION

Hypertension complicates up to 10% of all pregnancies and is associated with increased risk of adverse fetal, neonatal and maternal outcomes, including preterm birth, intrauterine growth restriction, perinatal death, acute renal or hepatic failure, antepartum haemorrhage, postpartum haemorrhage and maternal death [1,2]. Pregnancy hypertension (also known as pregnancy-induced or pregnancy-associated hypertension) has its onset from 20 weeks of gestation and ranges from hypertension alone (gestational [non-proteinuric] hypertension) through proteinuria and multi-organ dysfunction (preeclampsia) to seizures (eclampsia) [3-5]. Preeclampsia may be superimposed on pre-existing chronic hypertension. Although preeclampsia represents the severe end of the spectrum, women with any form of pregnancy hypertension are at increased risk of adverse outcomes [6,7].

Risk factors for pregnancy hypertension and preeclampsia have been well documented [2,7-13]. Factors that increase risk include nulliparity, older maternal age, multiple births, diabetes, chronic hypertension, obesity, previous preeclampsia, family history of preeclampsia, a new partner and/or ≥10 years since last pregnancy, renal disease, and the presence of antiphospholipid antibodies [2,7-9,11,13,14]. Decreased risk of pregnancy hypertension and preeclampsia has been associated with placenta praevia, smoking (although smoking may only be protective in the non-obese), summer births, low-dose aspirin and calcium supplementation in high-risk women, treatment of gestational diabetes and use of anti-hypertensive medications [2,9,10,12,15-19]. As the majority of cases of pregnancy hypertension and preeclampsia occur at term, increasing rates of early elective delivery may reduce their frequency [20-23]. Trends in pregnancy hypertension and preeclampsia are the result of the effects of changes in all these factors.

Population rates of pregnancy hypertension (based on routinely collected data) vary substantially in high-income countries, ranging from 4% to 10%, including preeclampsia rates of 2% to 5% [7,11,24-28]. At least part of this variation is likely due to under-ascertainment and/or misclassification of gestational hypertension and preeclampsia [29].

There are few recent reports of population trends in pregnancy hypertension [26-28]. International comparisons of *absolute population rates* of pregnancy hypertension and preeclampsia have been considered "virtually impossible" because of different diagnostic criteria and methods of data collection [30]. However, comparing *trends* between countries overcomes the difficulties in comparing absolute rates. Provided that methods of reporting do not change from year-to-year, temporal variations in each country reflect true changes in that country's rate of hypertension. The aim of this study was to determine and compare population-based trends in pregnancy hypertension and preeclampsia in high income countries.

METHODS

We used population health data (record-linked birth and hospital data where available) to determine pregnancy hypertension and preeclampsia rates in Australia, Canada, Denmark, Norway, Scotland, Sweden and the USA. We pre-specified that (1) participating centres had to provide a minimum of 6 years of data in the period from 1997 to 2007, and (2) if coding of hypertension was based on the *International Classification of Diseases (ICD),* the same ICD version had to be used for the entire period. The latter stipulation was made because preeclampsia coding in ICD-9 and ICD-10 are not comparable.

Study populations and data sources

The study populations included all women who gave birth (both live births and stillbirths) during the study period. Eight collaborating centres provided population health data on a regional or national basis, including: Australia (the states of New South Wales [NSW] and Western Australia [WA]), Canada (province of Alberta); Denmark, Norway, Scotland, Sweden and the USA (state of Massachusetts). Table 1 provides the average population, number of births and information on the data sources in the 8 study areas. The two Australian states account for approximately 43% of Australian births and together are referred to as 'Australia' in this paper. With the exception of the USA, all participating countries have universal health coverage for maternity care provided by midwives, general practitioners and obstetricians. Australia also has a parallel private health care system similar to that in the USA; about one-third of women seek private obstetric care.

Population health data were obtained from birth and/or hospital records in each study area. Birth data including information on maternal characteristics, pregnancy, labour, delivery and infant outcomes were collected by the attending midwife or doctor in a standard format. In Scotland, clinical coding staff within each hospital's medical records department extracted the birth data from all available medical records. Hospital data included demographic, administrative, and clinical data for all hospital discharges. Diagnoses and procedures for each admission were coded from the medical records according to the ICD. The number of diagnosis fields available in each medical record varied by study area, ranging from 6 to 25 (Table 1). However, a consistent numbers of fields were used within each country over the time period of the study.

Record-linked birth and hospital data were utilised in Australia, Denmark and Massachusetts. In Denmark the availability of a unique identifier allows unambiguous, deterministic linkage of records for each woman. In Australia and Massachusetts, unique identifiers are not available for record linkage. Consequently probabilistic linkage methods were utilised. This involves a complex process of blocking and matching combinations of selected variables (such as name, date of birth, address and hospital) using record-linkage software.[31] Probability weights are calculated, adjusted for incomplete and missing data, and used to determine correct matches. The validity of the probabilistic record linkage is extremely high with less than 1% of records having an incorrect match [31-34]. Once linked, and prior to release for analysis, records are stripped of identifying information.

Primary outcomes: pregnancy hypertension and preeclampsia

Population health data from each collaborating centre were used to estimate the overall incidence of any pregnancy hypertension (gestational hypertension, preeclampsia or eclampsia) and preeclampsia. During the study period, gestational hypertension was defined as the *de novo* onset of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) from 20 weeks' gestation onwards and preeclampsia as the *de novo* onset of hypertension from 20 weeks' gestation onwards accompanied by proteinuria [3].

Information on maternal hypertension status was available from birth and/or hospital data (Table 1). In the birth data, gestational hypertension, preeclampsia (in some cases by severity) and eclampsia data were generally collected as check-box fields and/or free text fields that were coded according to the ICD. In all hospital data, hypertension (as diagnosed by the attending clinician) was coded from the medical record according to the ICD. Because of

expected variations in reporting and/or coding, we made an *a priori* decision that the optimal identification of pregnancy hypertension and preeclampsia would be based on local knowledge of reporting methods and validation studies of hypertension reporting. We aimed to achieve the best and most consistent reporting in each study area. Since our focus was on trends over time, our key concern was to ensure that data collection and reporting within each study area were consistent over the study period. It was clear that differences in the baseline rates between study areas would be unavoidable.

Validation studies focusing on reporting of hypertensive disorders of pregnancy in birth and hospital data from Europe, North America and Australia have had remarkably consistent findings: pregnancy hypertension and preeclampsia are reliably and accurately reported in population health data [35]; ascertainment is improved when hypertension is identified from more than one data source (birth and hospital records for the birth admission or birth and antenatal records) [29,36]; preeclampsia is generally better ascertained and more accurately reported than gestational hypertension [24,25,29]; the broad category of 'any preeclampsia' is more reliably reported than subgroups stratified by severity [37,38]; similarly the broad category of pregnancy hypertension is more accurately reported than the subgroups of preeclampsia and gestational hypertension, with the possible exception of countries where ascertainment of gestational hypertension is known to be low (including Denmark and Sweden) [24,29,38,39].

Exposures

The collaborating centres provided information on maternal and pregnancy characteristics of the study populations including age, parity, smoking at registration and/or during pregnancy, ethnicity, overweight/obesity (BMI ≥25.00 kg/m^2), diabetes, chronic hypertension, multiple

gestation, induction of labour, mode of delivery and gestational age. Preterm birth (<37 weeks gestation) was categorised as spontaneous or elective (planned/elective caesarean section before the onset of labour or induced labour). Gestational age was reported in completed weeks, based on the best available estimate from ultrasound dating and/or menstrual history. The most reliable source (birth and/or hospital data) was used to determine exposures.

Approvals

The Publication Board at the Medical Birth Registry of Norway and the Danish Registry Board approved the study. In NSW, the record linkage was approved by the NSW Population and Health Services Research Ethics Committee (2006-06-011). No other permissions were required for analysis and presentation of the data.

Statistical Analyses

All analyses were based on women who delivered in each study location. We plotted secular trends in pregnancy hypertension and preeclampsia (per 100 deliveries per annum) for each study area based on available data over the study period. Temporal trends in numbers of pregnancy hypertension and preeclampsia events by study area were modelled using negative binomial regression. The covariance matrix was scaled by the deviance divided by the degrees of freedom and the additional variance component k estimated by maximum likelihood. Study year was fitted to the models, permitting estimation of yearly changes (with associated 95% confidence intervals) in numbers of events relative to baseline. Model fit (P>0.2 in all models) was assessed using the Pearson chi-squared goodness of fit statistic. Changes over time in population characteristics were analysed using the chi-squared test for trend with the significance level set at P<0.01.

RESULTS

Data were available from the 8 study areas for periods of 6 to 10 years between 1997 and 2007. The maternity populations ranged in size from an average of 25,000 per annum (pa) in Western Australia to 100,000 pa in Sweden (Table 1). Although not measured from the same starting time or for the same duration, significant changes in the absolute number of women giving birth were observed in some areas, with increases in Alberta (by +26%), Sweden (+17%) and Australia (+7%), and declines in Scotland (–6%), Denmark (–4%) and Massachusetts (–4%). In Norway, deliveries declined from 1999 to 2002 (–6%) and then gradually returned to baseline in 2006.

Details of maternal and pregnancy characteristics and trends for each population are presented in Table 2, highlighting some differences between study areas. The proportion of women delivering their first baby ranged from 40.7% in Norway to 45.2% in Scotland, and increased in all populations. Multiple gestation rates were higher in Massachusetts, which also had the highest proportion of mothers aged ≥35 years. The Nordic countries (Denmark, Norway and Sweden) had lower rates of deliveries among teenagers, comparatively low rates of medical induction and operative deliveries (vaginal instrumental and caesarean deliveries), and lower rates of preterm birth. Maternal age increased over time in the Nordic countries, Australia and Scotland. Smoking declined, and inductions and caesarean sections increased in most study areas. Where data were available, there was a downward shift in gestational age at term with an increasing proportion of infants born at 37-39 weeks. This was accompanied by an increase in preterm births in NSW and Denmark. Information on the proportion of women who were overweight or obese was only available in Sweden (35.5%) and Denmark (32.1%). In Sweden BMI information was available for 86% of women and in Denmark data were

available for 92% of women for 2004-2006, with no significant change in the rate of overweight or obesity during that period.

As anticipated, the reported rates of pregnancy hypertension (3.6% to 9.1%), preeclampsia (1.4% to 4.0%) and early onset preeclampsia (0.3% to 0.7%) varied between study areas. The contribution of preeclampsia to the pregnancy hypertension rate also varied from 23% in Alberta to 74% in Sweden (median=41%).

Figure 1 shows the trends in pregnancy hypertension rates for each study area. The average yearly rate decreased significantly during the study periods in 4 of the 8 areas. In Scotland pregnancy hypertension decreased by -6.2% per annum (pa) (95% CI -5.2%, -7.3%), in WA by -4.8% pa (95% CI -4.1%, -5.5%), in NSW by -4.1% pa (95% CI -3.4%, -4.8%), and in Sweden by -0.6% pa (95% CI -0.1%, -1.1%). There was no significant change in the rate of pregnancy hypertension in Alberta (p=0.43), Denmark (P=0.23) or Norway (P=0.90), while in Massachusetts the rate increased significantly by 2.3% pa (95% CI 1.9%, 2.7%)

Trends in preeclampsia (Figure 2) mirrored those of pregnancy hypertension in most study areas with significant decreases in NSW [-6.0% pa (95% CI: -4.2%, -7.7%)], Scotland [-3.0% pa (95% CI: -0.7%, -5.2%)], WA [-1.3% pa (95% CI: -0.3%, -2.3%)], and Sweden [-1.2% pa (95% CI: -0.6%, -1.8%). A significant increase was observed in Massachusetts [2.4% pa (95% CI: 1.5%-3.3%)]. Norway and Denmark experienced declines in preeclampsia rates [-2.5% pa (95% CI: -1.4%, -3.5%) and -0.7% pa (95% CI: -0.02%, -1.4%), respectively], despite the lack of significant reductions in pregnancy hypertension. In Alberta, the preeclampsia rate increased by 4.4% pa (95% CI: 2.4%-6.4%), albeit from a very low base

rate of 1.1%. Where data were available, the trends in pregnancy hypertension and preeclampsia were similar when analyses were restricted to nulliparous women.

DISCUSSION

Most countries saw a decline in the rates of pregnancy hypertension and/or preeclampsia over time. This was an unexpected result since factors thought to be positively associated with pregnancy hypertension such as pre-pregnancy overweight and obesity, diabetes, multiple births, and maternal age are generally recognised as increasing while smoking during pregnancy (associated with reduced rates of pregnancy hypertension) has decreased. Trends in these factors have been proposed as possible explanations for the increase in pregnancy hypertension and preeclampsia rates reported for the entire USA from 1987 to 1998 (although the rates plateaued from 1999 to 2004) [26]. In contrast, a study from Western New York based on a perinatal database from 1999 to 2003 reported significant declines in both pregnancy hypertension and preeclampsia [27].

As expected, we observed variation between study areas in baseline rates - more marked for pregnancy hypertension than for preeclampsia. However, for study areas with declining rates, the rates tended to converge over time. A significant part of the variation in baseline rates was likely related to differences in study population inclusion criteria and data recording methods. Although the lower gestational age boundary varied by country (gestational age 20-22 weeks or birth weight 350-500 g for live births and 20-28 weeks for stillbirths), the impact was likely to be small as pregnancy hypertension and preeclampsia most frequently occur in the third trimester [7,27,40]. Stillbirth, a complication of preeclampsia, is counted only from 28 weeks onwards in the Swedish data which may have reduced the country's rates. However, the number of stillbirths <28 weeks was low (<2/1,000 births) and similar hypertension rates

in Denmark (which included stillbirths in earlier weeks) argues against this as a significant explanation for observed differences in pregnancy hypertension rates. At the same time, validation studies from Denmark and Sweden indicated under-enumeration of gestational hypertension compared with preeclampsia, which would explain the high ratio of preeclampsia to gestational hypertension in these countries [24,25].

Variability in the age, parity, chronic disease, smoking and multiple birth distributions will also influence the baseline rates of pregnancy hypertension and preeclampsia [2,7,12]. Although data from Australia, the USA and Canada were from regional populations, these populations are likely to be more homogenous than the entire country populations and may be more similar to the European populations. Furthermore the regional populations will have fewer climatic differences than experienced by entire countries like the USA, Canada and Australia.

The period of available data is another factor influencing the pregnancy profiles. For example, caesarean section rates tended to be lower in countries reporting for longer time periods; shorter, more recent periods have the highest rates. Although national and international guidelines defining preeclampsia and pregnancy hypertension were consistent during the study period, changes to Australian and New Zealand guidelines in 2008 may cause a greater divergence in baseline rates in the future [2,3,41]. The inclusion of non-proteinuric hypertension with multi-organ disease in the clinical diagnosis of preeclampsia could increase the incidence of preeclampsia by up to 25%, but should not affect the overall rate of pregnancy hypertension [40].

Finally, hospital data in all study areas, except Massachusetts, were coded using the 10th revision of the ICD. Unlike ICD-9, ICD-10 combines mild preeclampsia with gestational hypertension. While this should not affect the reported rate of pregnancy hypertension, it reduces the rate of preeclampsia in ICD-10 compared with ICD-9. The change in NSW from ICD-9 in 1997 to ICD-10 in 1998 coincided with a shift from an increasing to a decreasing trend in pregnancy hypertension, suggesting the impact of the ICD version should not be disregarded. Furthermore, study areas with the highest rates of pregnancy hypertension (Australia and Massachusetts) have linked data and more diagnosis fields per record, characteristics shown to increase ascertainment in population data [29,36]. Combinations of all these factors, as well as differences in the population of pregnant women are likely contributors to differences in baseline rates between the study areas.

Although inconsistencies in diagnostic criteria, study populations, and temporal, geographic and demographic factors may explain differences in baseline rates, they do not explain the observed trends in pregnancy hypertension and preeclampsia. The year-to-year trends are influenced by the prevalence of risk factors in the study populations, prenatal care and therapeutic interventions. Many recognised risk factors for pregnancy hypertension and preeclampsia increased in all or some of our study populations during the study period, including nulliparity, advanced maternal age, diabetes, chronic hypertension and multiple pregnancy, while smoking rates (an apparent protective factor) declined everywhere. Diabetes, chronic hypertension and multiple pregnancy are associated with a 2- to 3-fold increase in risk of preeclampsia, but occur infrequently [2,9]. Small changes in the prevalence of these factors are unlikely to have a large impact on pregnancy hypertension rates in the population. While advanced maternal age and obesity are more common, the magnitude of risk is lower (less than double) [2,9]. Although only a few countries could provide

information on obesity in pregnant women, we assume that this is increasing in all participating countries, based on population trends.

Nulliparity provides perhaps the most contrary and puzzling disparity in preeclampsia trends. Nulliparity is common (42%-45%, increasing in most populations) and has a relative risk of preeclampsia estimated at 2.9 (95% CI 1.3-6.6) [9]. However, in our study, overall nulliparity rates did not correlate with the preeclampsia rates as expected. Instead, Scotland had both the lowest preeclampsia rates and the highest nulliparity rate, and Norway had the highest preeclampsia rates and the lowest nulliparity rate. Furthermore, the trends observed for all women were also observed amongst nullipara. Among multipara, preeclampsia in a prior pregnancy has been associated with a 7-fold increased risk in a subsequent pregnancy [9]. Although women with preeclampsia are also less likely to have another pregnancy, this does not explain the lower overall risk of preeclampsia in parous women [11]. Consequently, the impact of trends in parity on the population rates is complex and difficult to predict.

Changes in elective delivery (labour induction and caesarean section) are changing the distribution of gestational age at or near term. Increasing rates of early elective delivery before 40 weeks gestation have been reported internationally [20,22,23]. Almost 90% of pregnancy hypertension and over 70% of preeclampsia events occur at term, but fewer pregnancies are reaching 40 weeks or beyond [7,27,40]. Increasing rates of planned delivery of women with gestational hypertension could also explain why more study areas had decreases in preeclampsia rates [21]. Reducing the median length of gestation by even a few days could mean that a substantial number of women now deliver before they become hypertensive. It is also possible that utilisation of interventions that reduce the risk of pregnancy hypertension and/or progression to preeclampsia (such as low-dose aspirin, and

calcium supplementation, and possibly periconceptional multivitamin use in normal weight women) are contributing to the decline in hypertension rates [15,18,42,43].

A strength of our study is the quality of information collected from very different health systems. While variation may occur in reporting, completeness and validity of data, there were no major changes in data collection or reporting methods during the study period. Validation studies of the reporting of hypertension in pregnancy have been conducted in Australia, Canada, Denmark, Norway, Sweden and the USA with consistent findings about the reliability of each country's ascertainment methods [24,25,29,37-39,44]. This consistency is important when examining year-to-year variation.

In conclusion, we found declining rates of pregnancy hypertension and preeclampsia in northern Europe and Australia, a reassuring finding in the context of increasing maternal age, nulliparity and obesity. However, an increase in these rates was observed in Massachusetts. It is unclear whether the different ICD coding version used in the USA played a role in this finding. The role of elective delivery prior to the due date (especially late preterm and early term) in limiting the period of gestation during which the pregnancy hypertension and preeclampsia risks are greatest warrants further investigation.

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Competing interests statement

The authors declare that they have no competing interests.

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Authors' contributions

CLR and JBF conceived the project and developed the idea in collaboration with JMM, JC, JEN, JN, CJW. All authors (CLR, JBF, CSA, SA, JC, SC, MG, MK, KKM, AL, CM, JMM,

NN, JEN, JN, HTS, RW, CJW) contributed to study design, CLR, JC, SC, MK, KMM, NN, HTS and RW were responsible for data acquisition and CSA, SA, SC, MG, KKM, AL, CM, RW, CJW contributed to the analysis of data. CLR and JBF initially drafted the manuscript and all authors (CLR, JBF, CSA, SA, JC, SC, MG, MK, KKM, AL, CM, JMM, NN, JEN, JN, HTS, RW, CJW) were involved in critical revision of the intellectual content. All authors (CLR, JBF, CSA, SA, JC, SC, MG, MK, KKM, AL, CM, JMM, NN, JEN, JN, HTS, RW, CJW) approved the final manuscript.

Data Sharing Statement

The data are not available for sharing.

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Table 1: Population, birth numbers and data sources by study area

Maternal and pregnancy factors	Alberta Canada	NSW Australia	WA Australia	Denmark	Norway	Scotland	Sweden	Massachusetts USA
Total population	3.7 million	7.0 million	2.2 million	5.5 million	4.9 million	5.1 million	9.2 million	6.5 million
Births per annum	~42,000	~90,000	~25,000	~66,000	~60,000	~58,000	~100,000	~80,000
Inclusion criteria	Live and stillbirths ≥20 wks	Live and stillbirths ≥20 wks or ≥400g	Live and stillbirths ≥20 wks or ≥400g	Live and stillbirths ≥22 wks	Live and stillbirths ≥22 wks or ≥500g	Live and stillbirths	Live births ≥22 wks Stillbirths ≥28 wks	Live and stillbirths >20 wks or >350 g
Source of population data	DAD (H), BRVS (B)	APDC (H), MDC (B)	HMDS (H), MNS (B)	DNRP DMBR	MBRN	SMR02	SMBR	PELL
Linkage method	NA	Probabilistic	Probabilistic	Deterministic	NA	NA	NA	Probabilistic
Source of hypertension data	H	B and/or H	B and/or H	H	B	B	B	B and/or H
No. of diagnosis fields for hypertension reporting (data source)	25 (H)	11 (H) Checkbox(B)	21 (H) Checkbox(B)	20 (H)	Check-boxes and free text (B)	6 (B)	12 (B)	15 (H) Check-box (B)
ICD version	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-9
ICD codes for hypertension Pregnancy hypertension - Preeclampsia	 O11, O13-16 O11, O14-15	 O11, O13-16 O11, O14-15	 O11, O13-16 O11, O14-15	 O11, O13-15 O11, O14-15	 O11, O13-15 O11, O14-15	 O11, O13-16 O11, O14-15	 O11, O13-16 O11, O14-15	 642.3-642.9 642.4-642.6

H= Hospital data; B=Birth or obstetric data, NA=Not Applicable

DAD= Discharge Abstract Database; BRVA= Birth Registry of Vital Statistics; APDC=Admitted Patient Data Collection, MDC=Midwives Data Collection; HMDS=Hospital Morbidity Data System; MNS=Midwives' Notification System; DNRP=Danish National Registry of Patients; DMBR= Danish Medical Birth Registry MBRN=Medical Birth Registry of Norway; SMR02=Scottish Morbidity Record 2; SMBR= Swedish Medical Birth Register; PELL= Pregnancy to Early Life Longitudinal Data System

Table 2: Population characteristics by study area

Maternal and pregnancy factors	Alberta Canada N=256,137 %	NSW Australia N=732,288 %	WA Australia N=149,624 %	Denmark N=645,993 %	Norway N=456,353 %	Scotland N=531,622 %	Sweden N=913,779 %	Massachusetts USA N= 762,723 %
Study period	2002-2007	1998-2006	2000-2005	1997-2006	1999-2006	1997-2006	1997-2006	1998-2007
Maternal age (years								
<20	5.8	4.3†	4.6†	1.6†	2.4	8.3†	1.8	6.5
20-34	79.5	76.7†	75.2†	82.6	81.7	74.6†	80.1	71.5
≥35	14.7	19.0*	20.2*	15.8*	15.9*	17.1*	18.1*	22.0
Nullipara	44.2*	41.6*	41.6*	42.9*	40.7*	45.2*	43.9*	44.6
Multiple births	1.6[1]	1.6*	1.7	1.5*	1.9	1.5	1.5†	2.3
Diabetes (any)	4.0	5.4*	4.3	1.7*	1.5*	0.8	1.3	5.3
- Gestational diabetes	3.5	5.0*	3.8	1.3	0.8*	0.5	0.9	4.4
- Pre-existing DM	0.5	0.4*	0.6	0.4	0.7*	0.4	0.4*	1.0
Chronic hypertension	0.4	1.2*	1.1	0.4*	0.6†	0.3	0.5*	1.6
Smoking	Not available	17.4†	19.3†	20.6[2]†	18.6[3]† 13.1[4]†	24.8†	10.7[5]†	12.3
Induction of labour	21.4†	24.6*	29.2*	12.4*	12.0*	25.8	17.8*	20.1
Mode of delivery								
- Normal vaginal	61.4†	64.8†	57.6	75.7†	77.3	65.3†	76.8†	66.5
- Instrumental	13.0†	10.4†	12.4	7.2*	8.1*	12.5	7.5	6.1
- Caesarean section	25.6*	24.7*	30.0*	17.1*	14.8*	22.2*	15.7*	27.4
Term births								
-≥40 weeks	40.1	49.6†	43.6†	54.1†	53.6†	54.4†	53.5†	
- 37-39 weeks	51.2	43.9*	48.8*	39.4*	40.0*	38.6*	40.8*	
Preterm births (all)	8.4	6.5*	7.6	6.5*	6.4	7.0	5.5	9.5
- elective –see below	2.5	2.5*	3.6*	1.3*	2.8	0.6[7]	1.6	Not available
- spontaneous	5.9	4.0	4.0	5.2	3.6	6.4	3.9*	
OUTCOMES								
Any pregnancy hypertension	6.0†	8.8†	9.1†	3.6	5.8	5.9†	3.9†	7.0*
- preeclampsia	1.4*	3.1†	2.9†	2.7†	4.0†	2.2†	2.9†	3.3*
- preeclampsia ≤34 wks	0.7[6]	0.3	0.6	0.3	0.4	0.3	0.4	0.6

Percentages may not add to 100 because of missing data.
* increasing and † decreasing over the study period, χ^2 for trend P<0.01; 1. Alberta – multiple birth data available for 98.5% of women; 2. Denmark – smoking data available for 96% of women; 3. Norway – daily smoking in the first trimester (available for 83% of women); 4. Norway – daily smoking in the last trimester (available for 78% of women); 5. Sweden –smoking data available for 93% of women; 6. Alberta – gestational age available for 2004-2007; 7. Scotland – elective caesarean sections only

Figure legends

Figure 1: International trends in pregnancy hypertension

Figure 2: International trends in preeclampsia

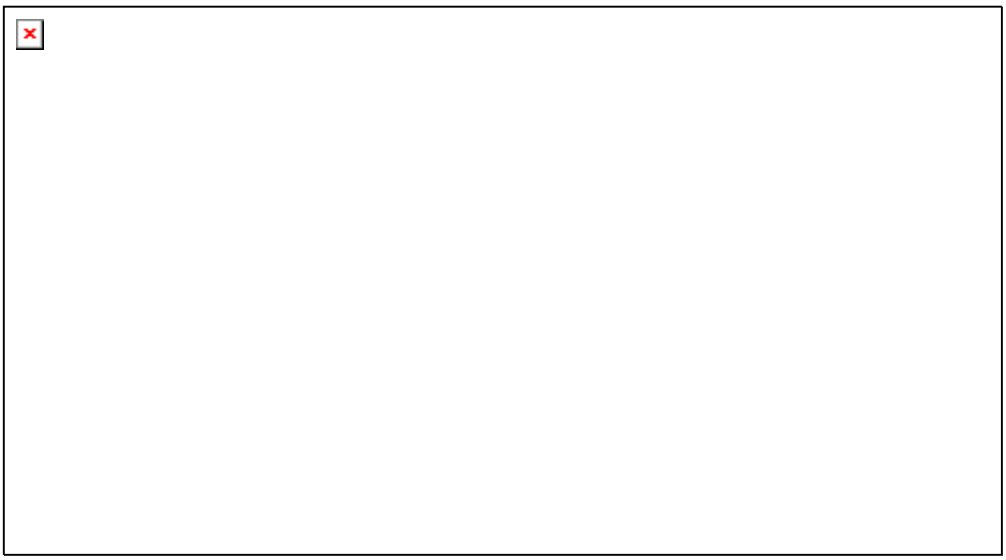
STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7, 22,24
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-8, 22
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8,22
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	NA (population data)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	24
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA (population data)

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	22-23
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	24
		(b) Indicate number of participants with missing data for each variable of interest	23
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10, 24
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figures 1 and 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



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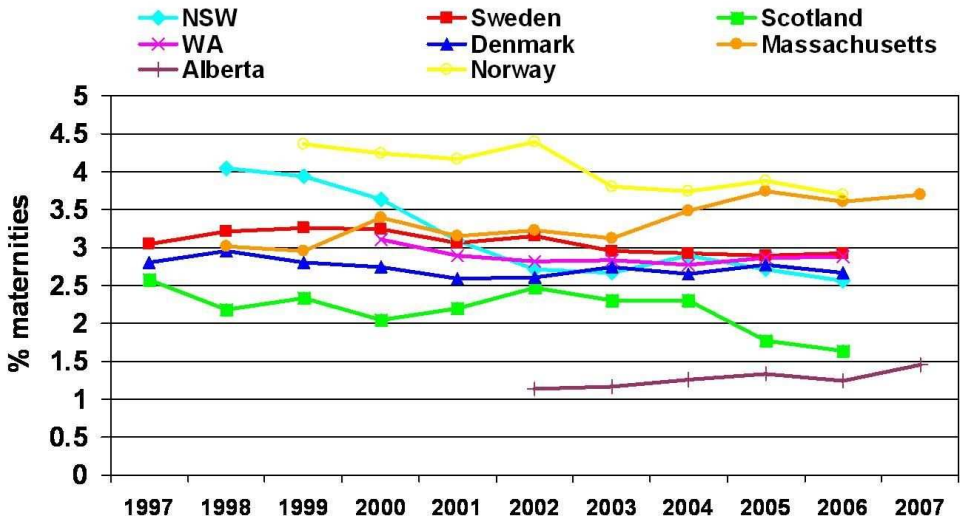

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